Physical activity and exercise interventions for disease-related physical and mental health during and following treatment in people with non-advanced colorectal cancer

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Physical activity and exercise interventions for disease-related physical and mental health during and following treatment in people with non-advanced colorectal cancer (Protocol)

McGettigan M, Cardwell CR, Cantwell MM, Tully MA

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[Intervention Protocol]

Physical activity and exercise interventions for disease-related physical and mental health during and following treatment in people with non-advanced colorectal cancer

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of exercise or physical activity interventions, or both, on the disease-related physical and mental health of individuals diagnosed with non-advanced colorectal cancer, staged as T1-4 N0-2 M0, treated surgically with or without neoadjuvant or adjuvant therapy (i.e. chemotherapy, radiotherapy or chemoradiotherapy).

BACKGROUND

Description of the condition

Colorectal cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide, accounting for an estimated 694,000 deaths in 2012 (Ferlay 2013). Incidence and mortality rates vary globally, with higher incidence and lower mortality rates in higher-income countries (Arnold 2015; Ferlay 2013; Stewart 2014). In general, incidence is higher in men than women and is strongly linked with age, with highest incidence among people aged 65 to 74 years (Howlader 2016). Incidence is currently stabilising in high-income countries, however a two-fold cumulative increase in incidence is expected by 2025, due to increasing incidence in low- to middle-income countries. With development, comes the adoption of more inactive lifestyles and unhealthy dietary habits; established risk factors for colorectal cancer (Stewart 2014). This is expected to increase the global burden of colorectal cancer, which may be compounded by a lack of health service resources in low- and middle-income countries to deal with the escalation in incidence (Stewart 2014).

Five-year survival from colon and rectal cancer has reached 60% or more in 22 countries worldwide (Allemani 2015). Between 1989 and 2011, colorectal cancer mortality rates decreased by more than 25% and 30% in men and women respectively in high-income countries in Northern and Western Europe but increased in most Eastern European countries (Ouakrim 2015). Similar trends are evident globally, with decreasing mortality rates in high-income countries, including Australia, Canada (Coleman 2011), the USA

(Ryerson 2016) and Japan (Arnold 2015), and contrasting increasing mortality rates in low- and middle-income regions, such as Latin America and the Phillipines (Arnold 2015). These disparities are not easily explained and are likely due to differences in access to diagnostic and treatment services (Haggar 2009), with advancements in treatment and early detection contributing to decreasing mortality in high-income countries (Coleman 2011; Stewart 2014).

Although treatments are advancing, anti-cancer therapies are associated with a range of adverse physiological and psychological side effects, which affect morbidity and mortality (Devin 2016). Surgical resection is the primary treatment modality for stage I-III (T1-4 N0-2 M0) colorectal cancer, with systemic chemotherapy or radiotherapy (more often in rectal cancer), or both, given either in the adjuvant or neoadjuvant setting in stage III and high-risk stage II patients (El-Shami 2015; Labianca 2010). Major abdominal surgery alone has been associated with declines in physical function (Schroeder 1991) and fatigue (Christensen 1982). Cancer-related fatigue affects between 60% to 96% of people with cancer during and following chemotherapy, radiotherapy or surgery (Cramp 2012; Thomas 2014; Wagner 2004). It is a distressing symptom defined as a sense of "physical tiredness or exhaustion related to cancer or cancer treatment" (NCCN 2016), which can interfere with one's ability to carry out daily activities (Curt 2000) and negatively affect mood and quality of life (Stone 2008). Cancer-related fatigue is present in some colorectal cancer survivors at four years following diagnosis (Schneider 2007). Physical inactivity has been identified as both a risk factor for (Bower 2014), and a consequence of (Lynch 2010) cancer-related fatigue.

Declines in cardiorespiratory fitness can occur following treatment for colorectal cancer (Devin 2016; West 2014a). Lower levels of cardiorespiratory fitness are linked with higher rates of cancer-specific morbidity and mortality (Peel 2009; Schmid 2015), and can predict morbidity after colonic (West 2014b) and rectal (West 2014c) surgery. Furthermore, people with colorectal cancer may be susceptible to sarcopenic obesity (obesity with depleted muscle mass), which is associated with poorer functional status and poorer survival rates (Prado 2008; Wang 2017). These adverse effects, alone or in combination can impact adversely on a patient's quality of life and subsequent physical activity levels (Cramer 2014a). Colorectal cancer survivors are also at an increased risk of developing second colorectal cancers (Green 2002; Markle 2010), non-colorectal cancers (Birgisson 2005) and other co-morbidities (Denlinger 2011).

Concerns surrounding recurrence are common, affecting over half of cancer patients at one year following diagnosis (Baker 2005). Even at five years following surgery for colorectal cancer, survivors have concerns surrounding recurrence (Custers 2016). A significant minority of colorectal cancer patients and longer-term survivors of colorectal cancer (two or more years post diagnosis) experience clinically meaningful levels of psychological distress, including symptoms of anxiety and depression or reduced mental well-being (Mosher 2016). Colorectal cancer survivors report high quality of life at five years or longer post diagnosis but have higher rates of depression than age-matched populations (Ramsey 2002). Psychological outcomes vary greatly in this population, poorer psychological outcomes have been linked with the presence of existing co-morbidities (Lynch 2008; Ramsey 2002), worse general health (Yost 2008) and lower socioeconomic status (Ramsey 2002). Levels of anxiety and depression are reported to be higher in people who undergo surgery with adjuvant chemotherapy or radiotherapy compared with surgery alone (Pereira 2012).

Description of the intervention

Exercise and physical activity interventions will be the focus of this review. Physical activity is defined as any bodily movement produced by contraction of skeletal muscle that results in energy expenditure above resting energy expenditure (ACSM 2009; Caspersen 1985). Exercise is a subset of physical activity that is planned, structured and repetitive, done to improve or maintain one, or more of the components of physical fitness (ACSM 2009; Caspersen 1985). Physical activity interventions may be less structured than exercise interventions and often focus on promoting the integration of activities into daily life (e.g. gardening, walking or active travel). Exercise and physical activity interventions may be self-directed or supervised by a healthcare professional. They can involve aerobic or resistance training, flexibility or balance training, or a combination of these, can take place in any setting and can be individual or group based, or both. No restrictions will be made regarding frequency, intensity, time or type of exercise or physical activity intervention included. Interventions will last a minimum of four weeks, to exclude studies on the acute effects of exercise or physical activity.

Exercise and physical activity interventions are not currently delivered as part of standard practice during or following treatment for colorectal cancer. Early postoperative mobilisation is, however, strongly recommended, as part of the Enhanced Recovery After Surgery (ERAS) guidelines following colorectal surgery, encouraging patients to be out of bed for two hours on the day of surgery and six hours per day, thereafter until discharge (Lassen 2009). The American College of Sports Medicine (Schmitz 2010), the American Cancer Society (Rock 2012) and the British Association of Sport and Exercise Science (BASES 2011) guidelines confirm that exercise can be safely performed during and following cancer treatment in the general cancer population. Specific guidance statements on exercise and physical activity interventions during and following treatment for colorectal cancer have not yet been published, due to lack of evidence on adverse effects and lack of safety data (Schmitz 2010). Side effects of treatments (cancer-related fatigue, peripheral neuropathy, immune suppression, digestion issues, bowel dysfunction (including faecal incontinence) and urinary incontinence) may increase the risk of adverse events during exercise and physical activity. These side effects may

represent barriers to exercise and physical activity participation (Denlinger 2009; Denlinger 2011; Rock 2012; Schmitz 2010). Indeed, chronic diarrhoea is a side effect that has been associated with limitations in activity and negative body image (Schneider 2007). The presence of a stoma is also associated with diminished body image (Hong 2014). These side effects have been highlighted as factors to consider when prescribing exercise or physical activity. Existing co-morbidities (most commonly cardiovascular disease, musculoskeletal problems and lung or breathing problems), particularly in older people with colorectal cancer have been highlighted as other factors requiring consideration, to reduce the risk of injury and adverse events (Denlinger 2009; Rock 2012; Schmitz 2010).

How the intervention might work

Physical activity and exercise have been proposed as non-pharmacologic interventions to attenuate the negative physiologic and psychologic effects of treatment in people with cancer (Courneya 2007; Schmitz 2005). There is a growing body of evidence from Cochrane and non-Cochrane systematic reviews demonstrating the positive impact of physical activity and exercise both during and following cancer treatment (Galvao 2005; Knols 2005; Schmitz 2005; Speck 2010). Exercise training improves cardiorespiratory fitness and muscle strength (Schmitz 2005; Speck 2010), overall health-related quality of life (HRQoL) (Knols 2005; Mishra 2012a; Mishra 2012b), and cancer-related fatigue (Cramp 2012; Furmaniak 2016; Speck 2010) in the general cancer population during and following cancer treatment, and physical functioning during treatment (Mishra 2012a). Through improved cardiorespiratory fitness and muscle strength, physical activity and exercise may help address the physical deconditioning associated with cancer treatments (Speck 2010; Schmitz 2005) and help manage cancer-related fatigue (Al-Majid 2009; Cramp 2012). Physical activity and exercise may also help the emotional and mental aspects of cancer-related fatigue (Al-Majid 2009; Cramp 2012). Benefits of exercise interventions on psychological well-being (Knols 2005), anxiety and depression show positive trends but the evidence is not consistent (Cramp 2012; Furmaniak 2016; Mishra 2012a).

Cardiorespiratory fitness has been highlighted as an independent predictor of cancer mortality risk. Higher cardiorespiratory fitness is associated with a significant reduction in total cancer mortality (Schmid 2015) and colorectal cancer mortality (Peel 2009). Peel and colleagues report that men with at least a moderate fitness level had a 42% lower risk of colorectal mortality compared with men with a low cardiorespiratory fitness level. Evidence from observational studies suggest that physical activity is associated with overall and disease-free survival (Haydon 2006; Meyerhardt 2006; Meyerhardt 2009) in both colon and rectal cancer patients.

There is consistent evidence linking physical activity to reduced colon cancer risk (Leitzmann 2015; Wolin 2009). A meta-analysis of 52 studies found an inverse association between physical activity and colon cancer, with an overall relative risk reduction (RR) of 24% (Wolin 2009). This is consistent with findings of an earlier meta-analysis of 19 cohort studies, which demonstrated a lower risk of colon cancer of 22% and 29% in physically active men and women respectively (Samad 2005). Conversely, there appears to be no consistent association between physical activity and rectal cancer risk (Robsahm 2013).

The exact biological mechanisms for the observed benefit of physical activity and exercise for the prevention and secondary prevention of colorectal cancer are not fully understood. Various mechanisms have been proposed. Physical activity and exercise may reduce carcinogen exposure in the mucosa through decreased gastrointestinal transit time (Quadrilatero 2003; Slattery 2003), may alter prostaglandin levels (prostaglandins are unsaturated, free fatty acids that affect colonic function) (Quadrilatero 2003) and may alter the insulin-like growth factor (IGF) pathway (Denlinger 2011; Fairey 2003). In people with colorectal cancer, moderate-intensity exercise has resulted in reduced levels of urinary markers of oxidative damage (Allgayer 2008) and decreased interleukin-1 receptor agonist (Allgayer 2004), which may enhance immune function. Oxidative DNA damage is thought to be involved in tumour formation and may be associated with malignant transition and recurrence (Allgayer 2008). IGF-1 is important for cellular proliferation and survival (Hursting 2010), higher levels of which may be associated with increased risk of colorectal cancer (Giovannucci 2000), but this association remains elusive. Decreases in IGF and increases in IGF-binding proteins have been observed following exercise training in breast cancer survivors, which may be clinically relevant for the colorectal cancer population (Fairey 2003)

Physical activity and exercise may therefore be potentially effective in improving overall and disease-free survival. Indeed, given that regular physical activity can decrease the risk of colon cancer and has improved cardiorespiratory fitness, muscle strength, HRQoL and cancer-related fatigue in other cancer populations, it may be of clinical relevance for the colorectal cancer control continuum.

Why it is important to do this review

Colorectal cancer is a major public health problem. With the projected increasing incidence of colorectal cancer in developing regions, the increasing mortality rates in low- and middle-income countries and 3.5 million colorectal cancer survivors worldwide (Stewart 2014), there is a requirement to develop effective interventions that aid physical and psychological recovery, help alleviate treatment side effects and increase overall and recurrence-free survival. The Lancet Oncology commission have prioritised the reduction in morbidity and mortality associated with cancer, with a focus on "less toxic", "cost effective" interventions (Sullivan 2011). There is therefore a need for a greater understanding of the effects of exercise and physical activity interventions on the

disease-related physical and mental health of individuals with colorectal cancer, for policy, practice and for consumers.

To date, there is one published non-Cochrane systematic review on exercise interventions for people with colorectal cancer that complements this review (Cramer 2014b). No recommendations regarding exercise as a routine intervention for people with colorectal cancer were made following this review due to insufficient evidence and lack of safety data. The review undertaken by Cramer and colleagues was limited to individuals who had completed treatment. This review will be broader, and will include those who are receiving adjuvant therapy in addition to those who have finished treatment, in which there has been no previous review undertaken. This review is important in order to update current evidence and include emerging evidence in relation to exercise and physical activity interventions for individuals with colorectal cancer and to identify current evidence gaps.

OBJECTIVES

To assess the effectiveness and safety of exercise or physical activity interventions, or both, on the disease-related physical and mental health of individuals diagnosed with non-advanced colorectal cancer, staged as T1-4 N0-2 M0, treated surgically with or without neoadjuvant or adjuvant therapy (i.e. chemotherapy, radiotherapy or chemoradiotherapy).

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all randomised control trials (RCTs) and cluster-RCTs comparing exercise or physical activity interventions, or both, to usual care or no exercise or physical activity intervention for inclusion in this review.

Types of participants

We will include trials that evaluate the effect of exercise or physical activity interventions, or both, on adults (aged 18 years or over), regardless of gender, diagnosed with non-advanced colorectal cancer, staged as T1-4,N0-2, M0, treated surgically with or without neoadjuvant or adjuvant therapy (i.e. chemotherapy, radiotherapy, chemoradiotherapy). We will include trials that examine exercise or physical activity interventions, or both, delivered during adjuvant therapy, following adjuvant therapy or following surgery alone. We will exclude studies including participants with other cancer types, unless outcomes for colorectal cancer are reported separately and trials including participants who are more than five years post-diagnosis.

Types of interventions

We will compare exercise and physical activity interventions separately to either no exercise or physical activity intervention or to usual care. Participants in both the control and intervention arms will receive the same usual care. Exercise or physical activity sessions can take place in any setting, be supervised, self-directed or both, can be individual or group based, or a combination of both. Exercise or physical activity modalities can include aerobic or resistance training, flexibility and balance training or a combination of these. No restrictions will be made regarding frequency, intensity, time or type of exercise or physical activity intervention. We will only include studies with interventions that last a minimum of four weeks in duration, to exclude studies on the acute effects of exercise or physical activity. We will record specific details on the intervention according to the FITT-VP (frequency intensity, time, type, volume, progression) principle (ACSM 2014). We will classify exercise or physical activity intensity as mild, moderate or vigorous based on the rate of perceived exertion (RPE), heart rate (HR) or metabolic equivalents (METS) (ACSM 2014), and use the author's classification of mild, moderate, or vigorous when a quantitative measure is unavailable.

Types of outcome measures

We will extract information for the primary and secondary outcomes at all available time points. We will seek to analyse overall survival and recurrence-free survival at 12 months, 3 years and 5 years. We will seek to analyse the other primary and secondary outcomes according to the length of follow-up: up to 12 weeks after baseline (immediate); more than 12 weeks but less than 6 months after baseline (short term); more than 6 months but less than 12 months after baseline (medium term) and more than 12 months after baseline (long term).

Primary outcomes

1. Physical function (e.g. the Karnofsky Performance Status Scale; the Eastern Cooperative Oncology Group Scale; percentage of predicted peak oxygen uptake ($V0_2$ peak), timed chair rise test; timed 'Up & Go' test) or other valid instruments
2. Disease-related mental health (e.g. the Hospital Anxiety and Depression Scale; the Beck Depression Index)
3. Adverse events (participants experiencing at least one adverse event e.g. injury, death, adverse events resulting in discontinuation of the intervention)

Secondary outcomes

1. Overall survival (time interval between enrolment in the study and death of the person from any cause)
2. Recurrence-free survival (time interval between date of enrolment in the study and the date when colorectal cancer recurs or another cancer occurs during the follow-up)
3. Physical fitness (e.g. cardiorespiratory endurance (six-minute walk test; 10-metre shuttle walk test; $V0_2$ peak or muscle strength (dynamometry; one repetition maximum; five repetition maximum) or another valid instrument
4. Cancer-related fatigue (e.g. the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); the Schwartz Cancer Fatigue Scale (SCFS); the Brief Fatigue Inventory (BFI); the Piper Fatigue Scale (PFS))
5. Anthropometric measurements (e.g. weight, body mass index (BMI), body composition, waist measurement, skin-fold measurement)
6. HRQoL (e.g. the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30); the Medical Outcomes Study Short Form 36 General Health Survey (SF-36); the Functional Assessment of Cancer Therapy - Colorectal scale (FACT-C))
7. Levels of physical activity (e.g. physical activity questionnaires (International Physical Activity Questionnaire (IPAQ), Global Physical Activity Questionnaire (GPAQ)) or objective measures of physical activity using pedometers or accelerometers)

Search methods for identification of studies

Electronic searches

We will search the following electronic databases up to the latest issue with no language or date restrictions to identify relevant RCTs and cluster-RCT's or this review:

1. The Cochrane Central Register of Controlled Trials (CENTRAL, in the Cochrane Library) (Appendix 1) (inception to present)
2. Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to Present) (Appendix 2)
3. Ovid Embase (1974 to present) (Appendix 3)
4. CINAHL (in EBSCOhost 1982 to present)
5. Web of Science (1970 to present)
6. PsycINFO (1806 to present)
7. Open Grey (formerly SIGLE) (1980 to present)
8. PEDro (1999 to present)

Cochrane Colorectal Cancer's Information Specialist will conduct and verify the searches.

Searching other resources

We will search clinical trials registries separately for ongoing trials and trial protocols including:

1. Clinical.trials.gov (www.clinicaltrials.gov)
2. The World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/)
3. The EU Clinical Trials Register (www.clinicaltrialsregister.eu/)
4. CenterWatch (www.centerwatch.com)

We will screen reference lists of all included studies and any relevant systematic reviews identified. We will handsearch conference and meeting abstracts of relevant organisations including:

1. American Society of Clinical Oncology (ASCO)
2. European Society for Medical Oncology (ESMO)
3. American College of Sports Medicine (ACSM)
4. BIT's Annual World Cancer Congress
5. European Multidisciplinary Colorectal Cancer Congress (EMCCC)
6. European Federation for Colorectal Cancer (EFR)

We will contact individuals or organisations for information on unpublished or ongoing studies.

Data collection and analysis

Selection of studies

We will import all records retrieved from the searches into EndNote (Endnote 2016) and remove duplicated records.

Two review authors (MMG and MAT) will independently examine the studies identified in the literature search. Two review authors (MMG and MAT) will independently screen all studies based on their titles and abstracts and will remove studies that obviously do not meet the eligibility criteria. We will record reasons for exclusion and will not exclude studies solely on the basis of reporting of outcome data. We will obtain the full texts of potentially eligible studies and the two review authors (MMG and MAT) will independently examine the studies. The authors will code the studies as 'include', 'exclude' or 'uncertain' based on the outlined criteria. We will resolve any disagreements through discussion, where necessary involving a third review author (CC or MMC), and keep a record of decisions made.

Data extraction and management

Two review authors (MMG and MAT) will independently extract data from the studies that meet the inclusion criteria and will enter data in the Cochrane software Review Manager 5 (RevMan 5) (RevMan 2014) for analyses. We will record extracted data on a form pre-developed for this purpose. MMG and MAT will pilot the data extraction form in a random sample of three studies

to ensure it captures the required information. They will revise the form as required. We will resolve any disagreements through discussion, and where necessary refer to a third review author (CC or MMC). We will extract the following data.

1. Study details; author and year of publication, country of origin, aim, design, funding source, method of randomisation, method of recruitment, trial inclusion and exclusion criteria, duration of participation, conflicts of interest/ethical concerns, risk of bias assessment
2. Participant details; total number randomised, age, gender, cancer stage, type of cancer treatment, ethnicity, time since diagnosis, time beyond active treatment, baseline imbalances
3. Intervention details; exercise type, intensity, frequency, volume, setting, duration of intervention, supervised or self-directed, details of control/comparison intervention, adherence/contamination and co-interventions (e.g. medication use)
4. Outcomes; primary and secondary relevant to this review, including adverse events, follow-up time points, measurement tools used for outcomes, limits and direction of effect

Assessment of risk of bias in included studies

Two review authors (MMG and MAT) will independently assess each included study for risk of bias using the Cochrane 'Risk of Bias' tool (the *Cochrane Handbook for Systematic Reviews of Interventions,* Chapter 8.5.d, Higgins 2011a; Higgins 2017) (Appendix 4). We will assess random sequence generation, allocation concealment, blinding of personnel and outcome assessment, completeness of outcome data, selective outcome reporting as sources of bias and any other sources of bias and classify as 'high', 'low' or 'unclear'. Since it is not possible to blind participants to an exercise or physical activity intervention, we will only assess blinding in relation to study personnel and outcome assessors. We will resolve any disagreements through discussion and where necessary, through involving a third review author (CC or MMC). For each study, we will detail the risk of bias in table form along with a statement of justification for our judgement. We will summarise results in both a 'Risk of bias' summary figure and 'Risk of bias' graph (i.e. bar chart). When interpreting treatment effects, we will take into account the risk of bias for studies that contribute to that outcome.

Measures of treatment effect

For continuous outcomes (physical function, mental health, physical fitness, cancer-related fatigue, anthropometric measurements, levels of physical activity and HRQoL) we will determine the mean differences (MD) or standardised mean differences (SMD) (in cases where different instruments are used to measure the selected outcome), in the intervention group compared with the control with 95% confidence intervals (CIs). We will extract data for final scores and change from baseline scores, if available.

For time-to-event outcomes (overall survival and recurrence-free survival) we will extract hazard ratios (HRs) with standard errors, assuming that the HR is constant over time to compare the risk of death or recurrence of cancer in the treatment group with that in the control group. Where HRs are not presented, we will estimate them from reported data (e.g. Kaplan-Meier curves, logrank observed minus expected events and the logrank variance) using methods described by Tierney and colleagues (Tierney 2007).

For dichotomous outcomes (adverse events) we will calculate the risk ratio (RR) at individual study level by dividing the risk of an event in the intervention group by the risk of the event in the control group. We will define RRs greater than 1.0 as favouring the control group (i.e. fewer adverse events in the control group) and RRs less than 1.0 as favouring the intervention group (Deeks 2017).

We will use a fixed-effect or random-effects model to calculate weighted mean differences (WMD) or weighted SMD, weighted HRs and weighted RRs with 95% CIs. We will use the random-effects model with inverse-variance weighting wherever possible due to the nature of exercise as a highly-varied intervention and use the fixed-effect model when there are few studies or if the studies are small with few events. In sensitivity analyses, we will investigate the effect of the choice of model (fixed-effect or random-effects) on the pooled estimate.

Unit of analysis issues

For parallel-group, individually randomised trials, the colorectal cancer participant will be the unit of analysis in each study. We will include cluster-RCTs, if identified. We will extract data when cluster-RCTs report appropriate analyses, adjusting for the sample size in each cluster. Where control of clustering has not been performed we will attempt to correct for the intervention effects of cluster-RCTs by reducing the size of each trial to its 'effective sample size', which is the number of the original sample size divided by the 'design effect'. We will calculate the design effect as 1 + (M-1)* ICC, where M is the average cluster size and ICC is the intra-cluster correlation coefficient as described in the *Cochrane Handbook for Systematic reviews of interventions* section 16.3.4 (Higgins 2011b). We will use an estimate of the ICC derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered unlikely.

For trials reporting multiple follow-up time points, we will conduct separate meta-analyses to reflect immediate (less than 12 weeks), short-, medium- and long-term periods of follow-up, if

appropriate. For immediate follow-up we will extract data closest to the 12-week follow-up time point. For short- and medium-term follow-up, we will extract data closest to the six- and 12-month follow-up time point, respectively. For long-term follow-up, we will extract the longest time interval.

For trials with multiple arms, we will include only relevant intervention arms. We will combine all relevant intervention arms into a single group and combine all relevant control arms into a single group, creating a single, pair-wise comparison.

Dealing with missing data

We will attempt to contact authors of the included studies to request missing data on outcomes, participants and summary data. We will document reasons for missing data (missing at random or missing not at random) and how they were addressed. We will assess the extent to which studies analysed data according to the intention-to-treat principle. We will assess the level of missing data for included studies by comparing the number of participants included in the final analysis with the proportion of all participants in each study. For studies at high risk of attrition bias, we will attempt to perform both the best-case and worst-case sensitivity analyses to assess the impact of missing data on the estimates of effect.

Assessment of heterogeneity

We will evaluate clinical heterogeneity by examining diversity in participant characteristics, physical activity and exercise intervention characteristics, colorectal cancer treatment and outcomes among trials. We will evaluate methodological heterogeneity by examining diversity in study designs and risk of bias. We will not pool clinically or methodologically heterogeneous trials. We will visually inspect forest plots and use the Chi^2 test to assess statistical heterogeneity (with a P value < 0.1). We will use the I^2 statistic to assess the percentage of variation across studies that is due to heterogeneity and not due to chance (Higgins 2003). We will tentatively regard heterogeneity as 'low' if I^2 is less than 49%, 'moderate', if I^2 is between 50% and 75% and 'high' if I^2 is more than 75% (Deeks 2017). We will investigate potential sources of statistical heterogeneity by reassessing diversity in characteristics of studies (participant, intervention, treatment and outcomes) and by means of subgroup and sensitivity analysis.

Assessment of reporting biases

If there are at least 10 studies included in a meta-analysis, we will visually inspect funnel plots for asymmetry to investigate potential publication bias or small-study effects. We will follow the recommendations in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* for any statistical testing of funnel plot asymmetry (Sterne 2017).

We will attempt to control for time-lag bias, location bias, citation bias and language bias by using a comprehensive search strategy without language or date restriction, that includes searching for unpublished studies and searching trials registers. We will control for multiple publication bias by identifying duplicate publications of the same study and grouping these together, listing them as one study. For studies published after 1 July 2005, we will screen the Clinical Trials Register at the WHO ICTRP for the trial protocols (apps.who.int/trialsearch) to evaluate whether selective reporting of outcomes is present (outcome reporting bias).

Data synthesis

We will pool results from comparable groups of trials using both fixed-effect and random-effects models, if appropriate. Whenever possible, we will use a random-effects model with inverse-variance weighting for meta-analyses (DerSimonian 1986) due to the nature of exercise as a highly-varied intervention. We will use a fixed-effect model when there are few studies or if the studies are small with few events. We will conduct a sensitivity analysis to investigate the effect of the choice of model (fixed-effect or random-effects) on the pooled estimate. MMG and CC will conduct statistical analysis using RevMan 5 (RevMan 2014). We will consider a two-sided P value of less than 0.05 as statistically significant. Where data aggregation is not possible due to heterogeneity, we will provide a narrative synthesis of study results. We will summarise the findings of the systematic review alongside an assessment of the quality of evidence for each individual outcome using the GRADE approach (GRADE Working Group 2004).

Subgroup analysis and investigation of heterogeneity

Where there is sufficient data, We will perform subgroup analysis of the effect of the intervention according to:

1. Exercise and physical activity intervention characteristics (using frequency, intensity, time, type, volume progression to calculate METS/hours per week)
2. Participant characteristics (gender, age (over 65 years or under 65 years))
3. Cancer stage ((T1-2, N0, M0), (T3-4, N0, M0),(T1-4, N1-2, M0))
4. Cancer type (colon or rectal)
5. Treatment stage (during or post treatment)
6. Treatment type (laparoscopic or open surgery, neoadjuvant therapy or no neoadjuvant therapy)
7. Time since diagnosis (zero to one year, two to three years, four to five years)

Sensitivity analysis

Where possible, we will undertake sensitivity analysis to assess the robustness of results. We will re-analyse data after excluding studies with high risk of bias and studies that have not performed an

intention-to-treat analysis. We will conduct sensitivity analysis to investigate heterogeneous results with the identification and removal of heterogeneous studies. We will conduct sensitivity analysis to investigate the effect of the choice of model (fixed-effect or random-effects) on the pooled estimate. For studies at high risk of attrition bias, we will conduct a best/worse case sensitivity analysis to assess the impact of missing data on the estimates of effect. If there are any assumptions for ICC value used in cluster-RCTs we will perform sensitivity analysis. Other sensitivity analysis may be undertaken during the review process, that are currently unforeseen.

Summary of findings

We will assess the overall quality of evidence of the main review outcomes using the (GRADE) approach in 'Summary of findings' table(s) (GRADE Working Group 2004). The 'Summary of findings' table(s) will highlight the overall quality of the body of evidence for the main review outcomes, using the GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, indirectness, imprecision and publication bias). We will use GRADEpro GDT 2015 software to prepare the 'Summary of findings' table. We have included a preliminary 'Summary of findings' table below. We will also present the results from the pre-specified Sensitivity analysis and Subgroup analysis and investigation of heterogeneity when appropriate in 'Summary of findings' tables.

Exercise or physical activity compared with control in adults with non-advanced colorectal cancer
Population: adults with non-advanced colorectal cancer treated surgically with or without neoadjuvant or adjuvant therapy
Settings: any setting
Intervention: aerobic or resistance training, flexibility or balance training or a combination of these lasting at least 4 weeks
Comparison: control intervention (usual care or no exercise or physical activity intervention)

Outcomes	Illustrative comparative risks (95% CI) *Assumed risk Corresponding risk Control group Exercise group	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
Physical function (measurement tool) Follow-up: up to 12 weeks					
Disease-related mental health (measurement tool) Follow-up: up to 12 weeks					
Adverse events (participants experiencing at least one adverse event) Follow-up: up to 12 weeks					
Overall survival (time interval between enrolment in the study and death of the person from any cause)					

(*Continued*)

Follow-up: 12 months					
Recurrence-free survival (time interval between date of enrolment in the study and the date when colorectal cancer recurs or another cancer occurs during the follow-up) Follow-up: 12 months					
Physical fitness (measurement tool) Follow-up: up to 12 weeks					
Cancer-related fatigue (measurement tool) Follow-up: up to 12 weeks					
Anthropometric measurements (measurement tool) Follow-up: up to 12 weeks					
Health-related quality of life (measurement tool) Follow-up: up to 12 weeks					
Levels of physical activity (measurement tool) Follow-up: up to 12 weeks					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk**(and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

We will justify and document our judgements about the quality of the evidence (high, moderate, low or very low) and incorporate them into the reporting of results for each outcome.

The GRADE system classifies the quality of evidence in one of four grades:

1. High quality: we are very confident that the true effect lies close to that of the estimate of the effect;
2. Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
3. Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
4. Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect;

The quality of evidence can be downgraded by one (serious concern) or two levels (very serious concern) for the following reasons:

1. Risk of bias;
2. Inconsistency (unexplained heterogeneity, inconsistency of results);
3. Indirectness (indirect population, intervention, control, outcomes); and
4. Imprecision (wide confidence intervals, insufficient sample size or number of events).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

Cochrane Central Register of Controlled Trials (CENTRAL): year, issue number in the Cochrane Library (searched day, month, year)

#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees
#2 ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) near/5 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or malignan*)):ti,ab,kw (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [Exercise] explode all trees
#5 MeSH descriptor: [Exercise Therapy] explode all trees
#6 MeSH descriptor: [Sports] explode all trees
#7 "physical fitness" (Word variations have been searched)
#8 (physical* near/5 (fit* or train* or activ* or endur* or exer*)):ti,ab,kw (Word variations have been searched)
#9 (exercis* near/5 (train* or physical* or activ*)):ti,ab,kw (Word variations have been searched)
#10 sport*:ti,ab,kw (Word variations have been searched)
#11 walk*:ti,ab,kw (Word variations have been searched)
#12 swim*:ti,ab,kw (Word variations have been searched)
#13 pilates*:ti,ab,kw (Word variations have been searched)
#14 tai ji or tai chi or tai-ji or tai-chi:ti,ab,kw (Word variations have been searched)
#15 resistance near/3 train*:ti,ab,kw (Word variations have been searched)
#16 #4 and #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
#17 #3 and #16

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to present (day, month, year)
1. exp colorectal neoplasms/
2. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj5 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or malignan*)).mp
3. 1 or 2
4. exp exercise/
5. exp exercise therapy/
6. exp sports/
7. Physical Fitness/
8. (physical* adj5 (fit* or train* or activ* or endur* or exer*)).ti,ab
9. (exercis* adj5 (train* or physical* or activ*)).ti,ab.

(*Continued*)

10. sport*.ti,ab.
11. walk*.ti,ab.
12. swim*.ti,ab.
13. pilates.ti,ab.
14. (tai ji or tai chi or tai-ji or tai-chi).ti,ab.
15. (resistance adj3 train*).ti,ab.
16. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 3 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. clinical trials as topic.sh.
23. randomly.ab.
24. trial.ti.
25. 18 or 19 or 20 or 21 or 22 or 23 or 24
26. exp animals/ not humans.sh.
27. 25 not 26
28. 17 and 27

Appendix 3. Embase search strategy

Ovid Embase: 1974 to year week
1. exp large intestine tumor/
2. ((colorect* or colon* or rect* or anal* or anus* or intestin* or bowel*) adj5 (carcinom* or neoplas* or adenocarcinom* or cancer* or tumor* or tumour* or sarcom* or malignan*)).mp
3. 1 or 2
4. exp exercise/
5. exp sport/
6. physical fitness/
7. exercise therapy/
8. (physical* adj5 (fit* or train* or activ* or endur* or exer*)).ti,ab
9. (exercis* adj5 (train* or physical* or activ*)).ti,ab.
10. sport*.ti,ab.
11. walk*.ti,ab.
12. swim*.ti,ab.
13. pilates.ti,ab.
14. (tai ji or tai chi or tai-ji or tai-chi).ti,ab.
15. (resistance adj3 train*).ti,ab.
16. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 3 and 16
18. CROSSOVER PROCEDURE.sh.
19. DOUBLE-BLIND PROCEDURE.sh.
20. SINGLE-BLIND PROCEDURE.sh.
21. (crossover* or cross over*).ti,ab.
22. placebo*.ti,ab.
23. (doubl* adj blind*).ti,ab.

(*Continued*)

24. allocat*.ti,ab.
25. trial.ti.
26. RANDOMIZED CONTROLLED TRIAL.sh.
27. random*.ti,ab.
28. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. (exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans or man or men or wom?n).ti.)
30. 28 not 29
31. 17 and 30

Appendix 4. Criteria for judging risk of bias in the 'Risk of bias' assessment tool

Random sequence generation **Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence**	
Criteria for a judgement of 'low risk' of bias	The investigators describe a random component in the sequence generation process such as: • referring to a random number table; • using a computer random number generator; • ·coin tossing; • ·shuffling cards or envelopes; • throwing dice; • drawing of lots; • minimisation*. *Minimisation may be implemented without a random element, and this is considered to be equivalent to being random
Criteria for the judgement of 'high risk' of bias	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • sequence generated by odd or even date of birth; • sequence generated by some rule based on date (or day) of admission; • sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-

(*Continued*)

	random categorisation of participants, for example: • allocation by judgement of the clinician; • allocation by preference of the participant; • allocation based on the results of a laboratory test or a series of tests; • allocation by availability of the intervention
Criteria for the judgement of 'unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	
Criteria for a judgement of 'low risk' of bias	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • central allocation (including telephone, web-based and pharmacy-controlled randomisation); • sequentially numbered drug containers of identical appearance; • sequentially numbered, opaque, sealed envelopes.
Criteria for the judgement of 'high risk' of bias	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • using an open random allocation schedule (e.g. a list of random numbers); • assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • alternation or rotation; • date of birth; • case record number; • any other explicitly unconcealed procedure.
Criteria for the judgement of 'unclear risk' of bias	Insufficient information to permit judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement - for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	
Criteria for a judgement of 'low risk' of bias	Any one of the following: • no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;

(*Continued*)

	• blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'high risk' of bias	Any one of the following: • no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Criteria for the judgement of 'unclear risk' of bias	Any one of the following: • insufficient information to permit judgement of 'low risk' or 'high risk'; • the study did not address this outcome.
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors	
Criteria for a judgement of 'low risk' of bias	Any one of the following: • no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
Criteria for the judgement of 'high risk' of bias	Any one of the following: • no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
Criteria for the judgement of 'unclear risk' of bias	Any one of the following: • insufficient information to permit judgement of 'low risk' or 'high risk'; • the study did not address this outcome.
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data	
Criteria for a judgement of 'low risk' of bias	Any one of the following: • no missing outcome data; • reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • for dichotomous outcome data, the proportion of missing

(*Continued*)

	outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • missing data have been imputed using appropriate methods.
Criteria for the judgement of 'high risk' of bias	Any one of the following: • reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; • potentially inappropriate application of simple imputation.
Criteria for the judgement of 'unclear risk' of bias	Any one of the following: • insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided); • the study did not address this outcome.
Selective reporting Reporting bias due to selective outcome reporting	
Criteria for a judgement of 'low risk' of bias	Any of the following: • the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
Criteria for the judgement of 'high risk' of bias	Any one of the following: • not all of the study's pre-specified primary outcomes have been reported; • one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • one or more reported primary outcomes were not pre-

(*Continued*)

	specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
Criteria for the judgement of 'unclear risk' of bias	Insufficient information to permit judgement of 'low risk' or 'high risk'. It is likely that the majority of studies will fall into this category
Other bias Bias due to problems not covered elsewhere in the table	
Criteria for a judgement of 'low risk' of bias	The study appears to be free of other sources of bias.
Criteria for the judgement of 'high risk' of bias	There is at least one important risk of bias. For example, the study: • had a potential source of bias related to the specific study design used; or • has been claimed to have been fraudulent; or • had some other problem.
Criteria for the judgement of 'unclear risk' of bias	There may be a risk of bias, but there is either: • insufficient information to assess whether an important risk of bias exists; or • insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

MMG conceived the idea for the protocol, designed and drafted the protocol under supervision of MAT. MAT, MMC and CC contributed to the development of the protocol.

DECLARATIONS OF INTEREST

MMG: none known

CC: none known

MMC: none known

MAT: none known

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